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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Fomesafen

FROM: John A. Quest, Ph.D., Team Leader
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

JAQuest 8/27/86

TO: Robert Taylor, Product Manager #25
Fungicide Herbicide Branch
Registration Division (TS-769)

The Toxicology Branch Peer Review Committee met on July 24, 1986 to discuss and evaluate the data base on Fomesafen with particular reference to the oncogenic potential of the chemical.

A. Individuals in Attendance:

1. Peer Review Committee (Signatures indicate concurrence with peer review unless otherwise stated.

Theodore M. Farber
William Burnam
Richard Hill
Bernice Fisher
Robert Beliles
Judith Hauswirth
John A. Quest
Esther Rinde
Stephen Johnson
Robert Zendzian
Louis Kasza
Bertram Litt

2. Scientific Reviewers: (Non-Committee members responsible for presentation of data; signatures indicate technical accuracy of Committee report.)

Alan Katz

Marcia Van Gemert

3. Peer Review Committee Members in absentia: (Committee members who were not able to attend the discussion; Signatures indicate concurrence with the overall conclusions of the Committee).

Anne Barton

Reto Engler

Diane Beal

B. Material Reviewed:

The material reviewed consisted of a background summary of toxicology data on Fomesafen (Katz/Van Gemert memorandum of 6/27/86), copies of DER's of rodent oncogenicity studies and other toxicity studies, a listing of "one-liner" material on the Fomesafen data base, and other pertinent memoranda. A copy of the information reviewed is appended to this report.

C. Background Information:

Formesafen [5-(2-chloro-4-(trifluoromethyl) phenoxy)-N-methylsulphonyl-2-nitrobenzamide] is a postemergence herbicide (trade name, "Flex") that is manufactured by ICI Americas, Inc., Wilmington, Delaware. The attention of the Peer Review Committee was focused on the oncogenic potential of the chemical in CD-1 mice where an elevated incidence of benign and malignant liver tumors was reported in animals of both sexes. An oncogenic study in Wistar rats was also considered where no elevated tumor incidence was reported.

D. Evaluation of the Evidence:

1. Mouse Oncogenicity Study:

Fomesafen was administered in the diet to Charles River CD-1 mice for 2 years at dose levels of 0 ppm (128 mice/sex), 1 ppm (64 mice/sex), 5 ppm (64 mice/sex), 100 ppm (64 mice/sex) and 1000 ppm (64 mice/sex). An interim sacrifice period was conducted at 52 weeks involving 24 mice/sex in controls and 12 mice/sex in the treatment

groups. The study was conducted by Huntingdon Research Center, England. The following overall incidence pattern of liver tumors suggestive of a compound related effect were observed in male and female mice.

Liver Tumor Type	Sex	Dose (ppm) 0	1	5	100	1000
Adenoma	M	13/110(12%)	19/56(34%)[b]	5/52(10%)	17/54(31%)[a]	14/36(39%)[b]
Carcinoma	M	17/127(13%)	7/63(11%)	12/64(19%)	10/64(16%)	28/64(44%)[b]
Combined	M	30/127(24%)	26/63(41%)	17/64(26%)	27/64(42%)	42/64(66%)[b]
Adenoma	F	3/128(2%)	1/63(1%)	1/62(1%)	8/62(13%)[a]	12/48(25%)[b]
Carcinoma	F	0/128(0%)	1/64(1%)	2/64(3%)	2/64(3%)	16/64(25%)[b]
Combined	F	3/128(2%)	2/64(3%)	3/64(5%)	10/64(16%)[a]	28/64(44%)[b]

[a] = $p < 0.01$ compared to controls, Fisher's Exact Test
[b] = $p < 0.001$ compared to controls, Fisher's Exact Test

Liver tumors were statistically significantly elevated in mice of both sexes, as discussed below. In male mice, adenomas were elevated at 1, 100 and 1000 ppm and carcinomas were elevated at 1000 ppm. In addition, adenomas/carcinomas combined were increased at 1000 ppm. In female mice, adenomas were elevated at 100 and 1000 ppm and carcinomas were elevated at 1000 ppm. In addition, adenomas/carcinomas combined were increased at 100 and 1000 ppm. The above data indicate that there was a progression of benign tumors to malignant tumors in both sexes. The Committee also noted that some liver tumors (both adenomas and carcinomas) occurred at a 52- week interim sacrifice period at all dose levels in male mice, and at the high dose in female mice, indicating that there was a reduction in the time to tumor occurrence in male and female mice. An increase in liver hyperplasia, however, was not observed in treated mice. No historical control data on liver tumors in CD-1 mice from studies conducted at Huntingdon Center were available to the Committee.

A significantly increased rate of mortality occurred in male mice at the 100 and 1000 ppm dose levels and in female mice at the 1000 ppm dose level. For animals at the 1000 ppm level, this resulted in the sacrifice of all males at study week 79 and of all females at study week of 89. The deaths appeared related to liver toxicity (e.g., elevated alkaline phosphatase and SGPT levels were observed in these animals as early as study week 26). The

Toxicology Branch Statistical Team performed time-adjusted trend test analyses on the 1000 ppm male and female mice and found significant elevations in tumors at these early sacrifice periods.

A maximum tolerance dose (MTD) level appeared to be exceeded at doses of 100 and 1000 ppm in male mice, and at 1000 ppm in female mice, based on the increased mortality as well as changes in liver enzymes (increased alkaline phosphatase and SGPT), liver weight (increased weight), and liver pathology (eosinophilic hepatocytes and pigmented Kupffer cells/macrophages). A MTD level appeared to be approached at 100 ppm in female mice, based on increases in liver SGPT activity and liver weight. The Committee noted that liver tumors were observed at the two highest dose levels (1000 and 100 ppm) in males and females, and also at the lower dose level (1 ppm) in male mice which was below a MTD level.

2. Rat Oncogenicity Study:

Fomesafen was administered in the diet to Wistar (Alderley Park) albino SPF rats for 106 weeks. Groups of 52 males and 52 females were fed 0, 1, 5, 100 or 1000 ppm for 106 weeks (terminal sacrifice) and additional groups of 12 rats/sex were fed the same doses for only 52 weeks (interim sacrifice). The study was conducted by ICI Central Toxicology Laboratory. No oncogenic effects were noted in either male or female rats.

The highest dose level tested (1000 ppm) in male rats appeared to exceed a MTD level based on findings of reduced body weight gain, liver enzyme changes (increased alkaline phosphatase, alanine transaminase, aspartate transaminase, and hepatic aminopyrine N-demethylase activities), increased liver weight, and liver pathology (increased focal necrosis, pigment deposition in cells, and hyalinization of liver cells). The highest dose level tested (1000 ppm) in female rats approximated a MTD level. This dose was associated with increased hepatic aminopyrine N-demethylase activity, increased liver weight, and hyalinization of liver cells. The Committee noted that 90-day and 4-week subchronic studies of Fomesafen in rats supported the choice of 1000 ppm for use as a high dose level in the chronic study; the 1000 ppm dose in the subchronic tests produced toxic changes generally similar to those seen in the long-term test (see Section E.1.a. and E.1.b.).

E. Additional Toxicity Data:

1. Subchronic Toxicity Studies:

The Committee considered 3 subchronic studies. These included a 90-day study and a 4-week study in rats, and a 26 week study in dogs.

a. 90-Day Rat Study: Fomesafen was administered in the diet to 20 rats/sex/dose level at doses of 0, 1, 5, 100 and 1000 ppm. The LEL was 100 ppm in males and females based upon liver changes (increased alkaline phosphatase, alanine transaminase and aspartate transaminase levels; increased liver weights; increased hepatocyte hyalinization, hepatocyte eosinophilia, and increased peroxisomes), alterations in lipid metabolism (decreased triglyceride and cholesterol levels), and renal changes (increased kidney weight and reduced urinary protein). At the highest dose of 1000 ppm, all of the above changes plus a reduction in body weight gain occurred.

b. 4-Week Rat Study: Fomesafen was administered in the diet to 32 rats/sex/dose level at doses of 0 and 1000 ppm. Toxic changes induced by the chemical included liver changes (increased liver weight, eosinophilia, and increased peroxisomes) and alterations in lipid metabolism (decreased cholesterol, triglyceride and free fatty acid levels). Most of the changes were reversible within one week after treatment was discontinued.

c. 26-Week Dog Study: Fomesafen was administered in the diet to 6 dogs/sex/dose level at doses of 0, 0.1, 1 and 25 mg/kg/day. The LEL was 25 mg/kg/day in males and females based upon liver changes (increased weight, hepatocyte eosinophilia, and increased peroxisomes), alterations in lipid metabolism (decreased cholesterol and triglyceride levels) and renal changes (increased kidney weight and elevated BUN levels).

2. Metabolism:

Several metabolism studies were performed in Wistar rats using single oral or i.v. doses (5 mg/kg) of ^{14}C-Fomesafen. A sex difference was observed in the excretion of the chemical. That is, after oral dosing, males excreted more radioactivity (RA) in the feces (55%) than in the urine (34%), whereas females excreted more in the urine (75%) than in the

feces (23%). In bile duct cannulated rats, males also excreted more (RA) in the bile than did females (48-55% in males vs. 18-25% in females). The liver was also the major organ of RA accumulation in both sexes, but the RA concentration was greater in the male rat liver. Similar findings were observed in male and female rats following i.v. dosing with RA Fomesafen.

In another oral study in rats, elevation of the administered oral dose of ^{14}C-Fomesafen to 500 mg/kg led to a disappearance of the sex difference in excretion seen at the 5 mg/kg/day dose level. That is, excretion was similar in urine (74-79%) and feces (21-23%) of males and females.

In a separate metabolism study in dogs (single oral dose of 5 mg/kg of ^{14}-C labeled chemical), no sex difference in urinary, fecal, and biliary excretion was reported. Most of the administered RA was excreted in the urine (range of 47-83%), with the remainder in feces (range of 20-46%) and bile (range of 25-30%).

No metabolism studies on Fomesafen have been performed in mice.

3. Reproduction and Teratology Studies:

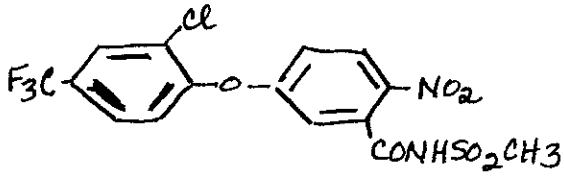
Three studies were reviewed by the Committee. In a 2-generation study in ALPK/AP/Wistar (SDF) rats, administration of Fomesafen in the diet at doses of 0, 50, 250 and 1000 ppm did not result in adverse reproductive effects. Changes reported in the male and female F_0 and F_1 parent animals were liver alterations (e.g. focal liver necrosis and Kupffer cell pigmentation) at 1000 ppm. Changes reported in the offspring consisted of decreases in litter weight gain (F_1a and F_1b males and females) at 1000 ppm, decreases in litter size (F_2a and F_2b litters) at 250 ppm or more, and also liver hyalinization (F_1b males) and renal pelvic dilation (F_2a males and females) at 1000 ppm. In a teratology study in Wistar (SPF) rats (oral doses of 0, 50, 100 and 200 mg/kg/day on gestation days 6-15), Fomesafen did not produce any teratogenic effects. The maternal toxic LEL was 200 mg/kg (increased post-implantation loss, decreased body weight) and the fetotoxic LEL was < 50 mg/kg (extra ribs, ossified skull bones and calcaneae, reduced fetal weight). In a teratology study in rabbits (oral doses of 0, 2.5, 10 and 40 mg/kg/day on gestation days 6-18), Fomesafen did not produce any teratogenic effects. The maternal toxic LEL was < 2.5 mg/kg (poor reproductive performance) and the fetotoxic LEL was 10 mg/kg (early deaths, partially ossified sternebrae).

4. Mutagenicity:

Six mutagenicity tests were performed with Fomesafen. Two of the tests were cytogenetic studies in rat bone marrow (one was performed in vitro and the other was performed in vivo), and Fomesafen was positive in both of these. In contrast, the chemical yielded negative results in several Ames tests (strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538) with and without metabolic activation, in a mammalian cell transformation test in baby hamster kidney fibroblasts, and in a dominant lethal assay in mice. Fomesafen also failed to bind covalently to rat liver DNA in vivo. In regard to the latter test, the Committee questioned whether the relatively low dose of Fomesafen tested and the low specific activity of the ^{14}C-labeled isotope might have rendered the assay insensitive, and therefore recommended that the protocol for the test be rereviewed by the Toxicology Branch scientist.

5. Structure-Activity Correlations:

Fomesafen is structurally related to 3 chemicals that are oncogenic in rodents. These are: 1) Acifluorfen (Blazer/Tackle) which produces hepatocellular adenomas and carcinomas in mice but which is negative in rats; 2) Nitrofen (Tok) which produces hepatocellular carcinomas in mice and pancreatic carcinomas in rats; and 3) Oxyfluorfen (Goal) which produces marginally positive liver tumors in mice but is negative in rats. These chemicals have not been evaluated by the Peer Review process; however, regulatory decisions based on their oncogenic potential have been made in the past.



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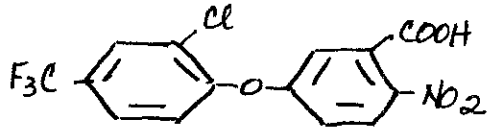

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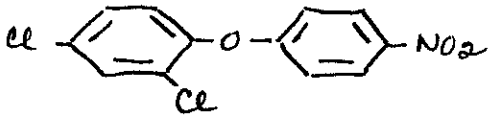

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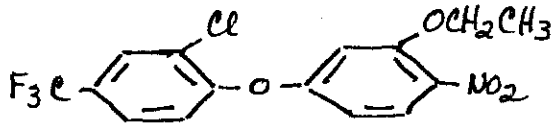

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F. Weight-of-the-Evidence Considerations:

The Committee considered the following facts regarding toxicology data on Fomesafen to be important in a weight-of-the-evidence determination of oncogenic potential.

1. Fomesafen, when administered in the diet to Charles River CD-1 mice, was associated with significantly elevated incidences of liver tumors (adenomas, carcinomas, and adenomas/carcinomas combined) in males and females. There was evidence, however, for a progression of benign tumors to malignancy, and for a reduction in the latency period for the-time-to-tumor appearance. There was no evidence for the occurrence of hyperplastic changes in the livers of treated mice.

2. Liver tumors were seen in male mice at dose levels (i.e., 100 and 1000 ppm) that exceeded MTD level, and also at a dose level (i.e. 1 ppm) that was below a MTD level. In addition, liver tumors were seen in female mice at a dose level (i.e. 1000 ppm) that exceeded a MTD level, and also also at a dose level (i.e. 100 ppm) that approximated a MTD level.

3. Fomesafen was not oncogenic when administered in the diet to Wistar albino rats at doses ranging from 1 to 1000 ppm. The highest dose tested in males (1000 ppm) in the chronic rat bioassay exceeded a MTD level, whereas this dose in females approximated the MTD.

4. The primary target organ of toxicity of Fomesafen in various non-chronic studies in several species other than mice (e.g., subchronic tests in rats and dogs, reproduction study in rats) was also the liver. Evidence of hepatocellular toxicity was also seen in the rat chronic bioassay of Fomesafen (where no tumors were observed).

5. No metabolism studies of Fomesafen were performed in mice. Studies conducted in rats, however, demonstrated a preferential concentration of the compound in the liver to the exclusion of other tissues. This finding is consistent with the liver being a target organ for Fomesafen toxicity.

6. Some evidence of genotoxic potential for Fomesafen was provided by positive findings in in vivo and in vitro cytogenetic tests in rat bone marrow. The

compound was found to be negative for genotoxic potential in another study (i.e., binding to rat liver DNA in vivo) but the acceptability of this test was questioned by the Committee (see section E.4).

7. Fomesafen bears a structural resemblance to other substances that have been demonstrated to be hepatocellular carcinogens in mice.

8. Fomesafen did not evoke adverse reproductive effects in rats and was not teratogenic in rats or rabbits.

G. Classification of Oncogenic Potential:

The Committee concluded that the data available for Fomesafen provided limited evidence of oncogenicity for the chemical in male and female CD-1 mice. According to EPA proposed guidelines (CFR, November 23, 1984), the Committee classified Fomesafen as a Category C oncogen (possible human carcinogen with limited evidence of carcinogenicity in animals in the absence of human data). That is, Fomesafen produced liver tumors (adenomas, carcinomas, and adenomas/carcinomas combined) at several dose levels in both sexes of CD-1 mice in a single experiment. In addition, there was some limited evidence for the mutagenicity of Fomesafen, and the compound was structurally related to known oncogens. The Committee also considered criteria for classifying a carcinogen in the B_2 category, but Fomesafen did not fully meet the criteria specified for this classification. This is, 1) it did not produce tumors in multiple species or strains; 2) it did not produce tumors in multiple experiments; and 3) it did not produce tumors to an unusual degree with regard to incidence or tumor site. There was a reduced latency period for the time to appearance of tumors in mice, but the Committee did not consider this finding to be of sufficient weight to elevate Fomesafen from the C to the B_2 category, particularly since the mouse liver tumor was the only oncogenic response observed.

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Chemical:	**Fomesafen**
PC Code:	**123802**
HED File Code	**21200 PEER REVIEW**
Memo Date:	**09/30/86 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0140**

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04/02/2004